UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/577,489	05/25/2000	Ray W. Wood	029318/0596	7761

31049 7590 05/07/2009

Elan Drug Delivery, Inc. c/o Foley & Lardner
3000 K Street, N.W.
Suite 500
Washington, DC 20007-5109

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
05/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/577,489	WOOD ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36, 39-40, 42-43, 51-60, and 64-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are pending. Applicants previously cancelled claims 1-27, 37-38, 41, 44-50, and 61-63. Applicants have amended claims 28-31 and 60. Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on January 14, 2009 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Priority

The Examiner kindly thanks Applicants for providing an Application Data Sheet (ADS) indicating Applicants' priority claims based on the instant application being a divisional of Application No. 08/948,216 (parent), which is a continuation of Application No. 08/589,681 (grandparent), which is a continuation-in-part of Application No. 08/394,103 (great-grandparent). Based upon the ADS, **the effective filing date of the instant application is February 24, 1995**.

Election/Restrictions

The species elections for asthma as the respiratory disease in a mammal and corticosteroids as the elected therapeutic agent are maintained and remain in effect.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over BECOTIDE® in view of Liversidge et al. (U.S. Patent No. 5,145,684) and Spear et al. (U.S. Patent No. 5,525,623), as evidenced by Radhakrishnan

(U.S. Patent No. 5,049,389) and "Glaxo History" (accessed October 24, 2008 at www.gsk.com/about/history-noflash.htm#).

Applicant Claims

Applicants claim a method treating a respiratory illness in a mammal comprising the steps of (a) providing an aerosol composition comprising aqueous droplets having a particle size of less than 10 microns in diameter, wherein the droplets comprise (i) water, (ii) crystalline particles of beclomethasone having an effective average particle size of less than 1,000 nm (i.e. at least 90% of the particles have a weight average particle size of less than about 1,000 nm, as defined on pg. 16, lines 24-27 of Applicants' specification), (iii) at least one surface modifier adsorbed on the surface of the crystalline beclomethasone particles, and (b) administering the aerosol composition to the lungs of a mammal, wherein the respiratory disease is selected from the group consisting of ***asthma***, emphysema, respiratory distress syndrome, chronic bronchitis, and cystic fibrosis.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

BECOTIDE® is **an aqueous suspension of beclomethasone dipropionate** that is administered via inhalation to treat asthma and was first made commercially available by Glaxo in 1972 ("Glaxo History"). Radhakrishnan was provided in part to demonstrate that BECOTIDE® is an aqueous suspension of beclomethasone dipropionate that is conventionally administered by nebulization (i.e. it is atomized from a nebulizer) to treat bronchial asthma (col. 5, lines 43-51). Radhakrishnan measured the liquid droplet particle size of aerosolized

BECOTIDE® expressed as mass median aerodynamic particle size (MMAD) in units of microns (Figure 4). Radhakrishnan also demonstrates that particles with a size of less than 1.1 microns read the alveoli upon inhalation (Figure 3). According to Radhakrishnan's measurements, approximately 15% of the droplets have a particle size of about 400 nm or less and ~ 95% of the liquid droplets have a size of 10 microns or less (Figure 4 and col. 16, line 53 through col. 17, line 17).

Liversidge teaches that dispersible particles consisting essentially **of crystalline poorly soluble drug substance having a surface modifier adsorbed on the surface thereof exhibit** unexpectedly higher bioavailability (title; abstract; col. 1, lines 5-10; col. 2, lines 34-37; and col. 3, lines 3-9). The **effective average particle size of the invented particles is less than about 400 nm** (abstract; col. 2, lines 38-43; col. 5, lines 25-40; claims 1-5). The phrase "**effective average particle size of less than about 400 nm" is defined to mean that at least 90% of the particles have a weight average particle size of less than about 400 nm** (col. 5, lines 25-28). **Preferably, at least 95% and more preferably, at least 99% of the particles have a particles size less than the effective average, such as 400 nm** (col. 5, lines 33-37). In some embodiments, the effective average particle size is less than about 100 nm (col. 5, lines 30-34). Suitable crystalline poorly soluble drugs include **anti-inflammatory agents and corticosteroids, and in preferred embodiments the drug substance is a steroid** (col. 3, lines 53-64; col. 4, lines 25-27; and claims 4-5). Suitable surface modifiers are disclosed from column 4, line 34 through col. 5, line 12 (e.g. sodium lauryl sulfate, lecithin, Pluronic F-68 [i.e. a polymer], etc.). The surface modifiers taught by Liversidge as being suitable are essentially ones recited in Applicants' laundry list in claim 32, for example. **Suitable amounts of surface**

modifier are taught to be about 0.1-10 mg per square meter surface area of the drug substance (i.e. 0.1-90% w/w, preferably 20-60% w/w, based on the total weight of the dry particle) (col. 7, lines 10-20).

Liversidge teaches **that the nanoparticles of crystalline drug substance may be obtained by conventional milling techniques, such as air jet and fragmentation milling** (col. 5, lines 50-61). Liversidge provides the necessary guidance to obtain nanocrystalline drug particles (see col. 5, line 41 through col. 7, line 29; claims 16-20). Liversidge teaches that the compositions may be delivered to mammals (e.g. claim 15).

Spear teaches that **jet nebulizers and ultrasonic nebulizers are conventional means of creating aerosols for use as asthma medication** (col. 13, lines 34-40).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

As far as can be ascertained at this time BECOTIDE® is silent as to the particle size and crystalline nature of the suspended beclomethasone dipropionate particles, as well as whether a surface active agent is adsorbed onto the surface of the crystalline beclomethasone particles and the quantity of surface modifier present. These deficiencies are cured by the teachings of Liversidge.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to combine the teachings of BECOTIDE® and Liversidge, because modification of BECOTIDE® per the teachings of Liversidge would yield a

inhalable pharmaceutical formulation comprising beclomethasone, which would reasonable exhibited a higher bioavailability. An ordinary skilled artisan would have also been motivated to modify BECOTIDE® to utilize nanometer-sized crystalline beclomethasone particles to ensure that these particles efficiently reached the alveoli upon inhalation, because sub-micron particle sizes are art recognized as being suitable for ensuring adminstration to the alveoli upon inhalation administration (e.g. see Fig. 3 of Radhakrishnan). Regarding the administration of BDP to treat asthma, BDP is a conventionally utilized to treat asthma, thus an ordinary skilled artisan would have been motivated to utilize BDP to treat a disease for which it is indicated.

Regarding the use of a jet nebulizer or an ultrasonic nebulizer to deliver the aqueous formulation, it would have been prima facie obvious to utilize a conventional nebulizer to administer formulations taught as being suitable for administration from a nebulizer, such as BECOTIDE®. An ordinary skilled artisan would have had a reasonable expectation of modifying BECOTIDE® per the teachings of Liversidge, because Liversidge provides the necessary guidance to obtain nanocrystalline BDP particles (see col. 5, line 41 through col. 7, line 29).

Regarding the amount of surface modifier present in the composition administered, the combined prior art teaches overlapping amounts of surface modifier. The combined prior art also teaches overlapping particle sizes and particle size distributions. A prima facie case of obviousness necessarily exists when the prior art range overlaps or touches a claimed range, such as in the instant rejection. MPEP § 2144.05. Furthermore, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious

for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Applicants' tabulated specification data is noted, and is not considered to demonstrate unexpected or surprising results. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Conclusion

Claims 28-36, 39-40, 42-43, 51-60, and 64-72 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.H.A.-A.
Patent Examiner
Technology Center 1600

/Johann R. Richter/
Supervisory Patent Examiner, Art Unit 1616